Genetic switch regulates transcription and replication in human mitochondria

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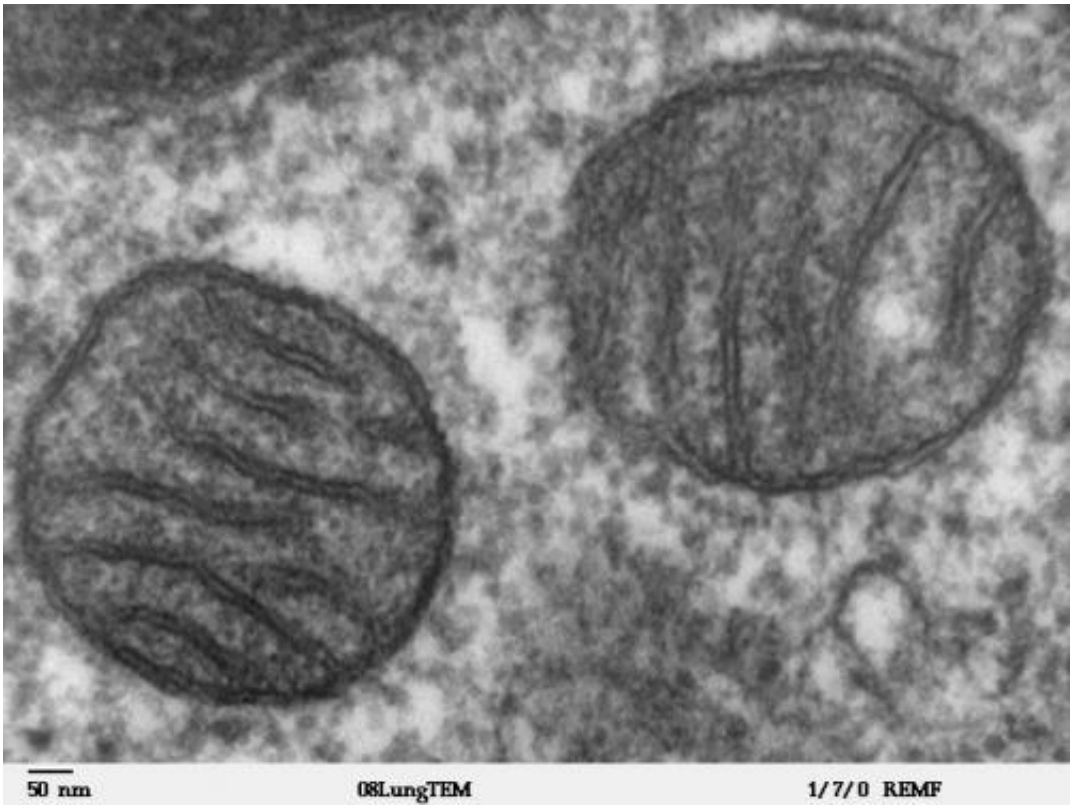

Mitochondria. Credit: Wikipedia commons

(Phys.org)—The majority of the human genome is located within the nucleus. However, there is a small but important portion of DNA located within the mitochondria. This mitochondrial DNA (mtDNA) has received much attention in the last few years for tracing ancestry, mitochondrial disease, and three-parent IVF. Mitochondrial DNA's

unique properties mean that it has different regulatory mechanisms. A new study by Dmitry Temiakov from Rowan University reports for the first time evidence that mtDNA transcription and replication are regulated by a molecular switch that may provide insight into developmental processes such as embryogenesis and spermatogenesis. The results are reported in *Science*.

Mitochondrial DNA, unlike nuclear DNA, undergoes transcription and replication at the same location. The transcriptional proteins used to read the mitochondrial RNA (mtRNA) strand, made from the mtDNA, are different from the ones used in replication but occur at the same time and space, which could potentially result in a collision and subsequent problems in gene expression. Temiakov's group investigated whether TEFM, a mitochondrial transcription elongation factor that has been shown to escalate transcription activity in promoterless DNA, plays a role in regulating transcription and replication in the mitochondria.

Transcription in the mitochondria occurs at two locations, the light strand promoter and the heavy strand promoter. Prior studies have shown that transcription terminates early, about 120 base pairs before the light strand promoter, at a region of mtDNA found in most vertebrates, known as CSBII, or conserved sequence block II. A hybrid complex forms with the nascent RNA and the nontemplate strand of DNA.

This complex forms near the origin of the of the replication primer for the heavy strand, and will replicate two-thirds of the mtDNA on the heavy strand. It stops near the origin of the light strand. The now single light strand forms a hairpin structure that is recognized by the mitochondrial RNA polymerase as the signal to begin replication of the light strand.

Temiakov's group showed that in the presence of TEFM, the

mitochondrial DNA polymerase does not stop at CSBII as it typically does in human mtDNA transcription, but continues transcribing through the CSBII section. Because TEFM prevents transcription termination, it also prevents the synthesis of the mtDNA polymerase primer that is used in replication. This finding provided one of several clues that TEFM acted to regulate replication and transcription in human mitochondrial DNA.

While conducting this study, the group inadvertently found that because their reference genome has a rare polymorphism in the CSBII region, they observed a decrease in efficiency of the transcription termination mechanism. They believe that the polymorphism disrupted the formation of the G-quadruplex, and that this G-quadruplex is involved in the CSBII mechanism.

Further investigations of how the G-quadruplex is involved in the TEFM mechanism showed that the TEFM interacts with the particular portions of the nascent RNA transcript. Temiakov's group believes that the TEFM interferes with the formation of the G-quadruplex, causing the hairpin structure to not form. This, in turn, does not signal to the mtRNA polymerase to begin replication.

Further studies showed that TEFM affects how well mtRNA polymerase is able to produce long transcripts. Without TEFM, shorter transcripts are formed, terminating at the CSBII region. TEFM increases processivity of mtRNA polymerase.

Temiakov concludes that TEFM serves as a switch that either "turns on" transcription, making it more efficient, or it "turns on" replication. This research indicates that replication and transcription are likely mutually exclusive processes in the human mitochondrial genome precluding the possibility that the transcription and replication processes will collide. Furthermore, this switch may be a key player in the developmental

processes in which transcription of mtDNA occurs but not replication.

More information: "Replication-transcription switch in human mitochondria" Karen Agaronyan, Yaroslav I. Morozov, Michael Anikin, Dmitry Temiakov, *Science*, vol 347, issue 6221, January 30, 2015, DOI: 10.1126/science.aaa0986

ABSTRACT

Coordinated replication and expression of the mitochondrial genome is critical for metabolically active cells during various stages of development. However, it is not known whether replication and transcription can occur simultaneously without interfering with each other and whether mitochondrial DNA copy number can be regulated by the transcription machinery. We found that interaction of human transcription elongation factor TEFM with mitochondrial RNA polymerase and nascent transcript prevents the generation of replication primers and increases transcription processivity and thereby serves as a molecular switch between replication and transcription, which appear to be mutually exclusive processes in mitochondria. TEFM may allow mitochondria to increase transcription rates and, as a consequence, respiration and adenosine triphosphate production without the need to replicate mitochondrial DNA, as has been observed during spermatogenesis and the early stages of embryogenesis.